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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,610	07/23/2001	Hagit Amitai	AMITAI 1	2065

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EXAMINER	
LI, RUIXIANG	
ART UNIT	PAPER NUMBER
1646	16

DATE MAILED: 05/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/807,610	Applicant(s) AMITAI ET AL.	
	Examiner Ruixiang Li	Art Unit 1646	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-12 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

I. Status of Application, Amendments, and/or Claims

The amendment filed in Paper No. 15 on February 26, 2003 has been entered in full. Claims 3-9 have been amended. Claims 13-15 have been canceled. Claims 1-12 and 16 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

II. Withdrawn Objections and/or Rejections

The objection to disclosure as set forth at page 3 of the previous Office action (Paper No. 14, November 26, 2002) has been withdrawn in view of applicants' amendment to the specification and argument. Applicants are right in that the first paragraph of the specification is not required to refer to the foreign application.

The rejection of claims 3-6 under 35 U.S.C. §101, as set forth at pages 3-4 of the previous Office Action (Paper No. 14, November 26, 2002), has been withdrawn in view of applicants' amendment to the claims.

III. Claim Rejections Under 35 U. S. C. § 101

The rejection of claims 9-12 and 16 under 35 U.S.C. §101, as set forth at pages 3-4 of the previous Office Action (Paper No. 14, November 26, 2002), remains.

Applicants argue that glycosylated icIL-1ra-II does not exist in nature. In nature, the protein is intracellular only and, thus, is not glycosylated. Glycosylation is part of the secretion mechanism (3rd paragraph of page 9 of applicants' response).

This has been fully considered but is not deemed to be persuasive because both Muzio et al. (J. Exp. Med. 182: 623-628, 1995; Abstract) and Colotta et al. (WO 96/12022, April 25, 1996; page 4, lines 22-24) teach that icIL-1ra-II is mostly intracellular. However, the possibility that icIL-1ra-II is glycosylated cannot be totally excluded. Thus, it is necessary to use the word "isolated" or "purified" to modify glycosylated icIL-1ra-II in order to avoid that the claims read on the product of nature.

IV. Claim Rejections Under 35 U. S. C. § 103(a)

(i) The rejection of claims 1-12 and 16 under 35 U.S.C. § 103(a), as set forth at pages 4-6 of the previous Office Action (Paper No. 14, November 26, 2002), remains.

(ii) Applicants argue that it is reasonably unpredictable whether or not the signal peptide of human growth hormone would drive the expression of icIL-1ra-II in a mammalian cell expression system because the icIL-1ra-II protein is naturally expressed only intracellularly and is not secreted from the cells, whereas the mature form of IL-1β is naturally secreted from the cells in which it is produced, although indirectly (page 11 of applicants' response).

This has been fully considered but is not deemed to be persuasive for the following reasons. First, as noted in the previous office action, it is routine for one skilled in the art to produce a secretory protein by fusion of a non-secretory protein with a

signal peptide of another secretory protein, as exemplified by Bjorkdahl et al, which is also acknowledged in the instant specification (page 3, lies 19-21).

Secondly, while mature form of IL-1β is naturally secreted from the cells in which it is produced, the pathway is different from the typical secretion pathway in mammalian cells. Pecceu et al clearly demonstrate that fusion of mature IL-1β to the signal peptide of human growth hormone allowed the protein to cross the membrane of rough endoplasmic reticulum and to follow the pathway of a typical secretory protein (page 257, bottom of left column to top of right column) and resulted in virtually complete secretion of a glycosylated form of IL-1β. Without the signal peptide of human growth hormone, only 52% of IL-1β was secreted via a distinct pathway (Table 1). In addition, transport of IL-1β to ER and Golgi apparatus after signal cleavage allowed full glycosylation (pages 256-257, section e). The mature form of IL-1β secreted **without** fusion to the signal peptide of human growth hormone was not glycosylated (bottom of left column to top of right column of page 257).

It is further noted that Muzio et al. teach that icIL-1ra-II is mostly intracellular (*IDS*, WO 9612022, April 25, 1996; page 4, lines 22-24), not as applicants have argued that icIL-1ra-II only intracellularly. The possibility that icIL-1ra-II is secreted or even glycosylated cannot be excluded.

Therefore, an artisan would be reasonably convinced and would expect that a non-secretory protein fused to the human growth hormone signal peptide would be glycosylated and secreted through the typical ER and Golgi apparatus secretory pathway.

(iii) Applicants argue that it would be expected that the secreted form of IL-1β would be biologically active after it is secreted as the mature form of IL-1β is naturally secreted (bottom of page 11), whereas icIL-1ra-II is strictly an intracellular protein. Thus, it could not have been reasonably predictable that this protein would still be active after being glycosylated and secreted (top of page 12).

This has been fully considered but is not deemed to be persuasive for the following reasons. First, the naturally secreted mature form of IL-1β is not glycosylated; whereas fusion of mature IL-1β to the signal peptide of human growth hormone resulted in virtually complete secretion of a glycosylated form of IL-1β, which was shown to be biologically active.

Secondly, the study of Muzio et al. (WO 96/12022, April 25, 1996; page 4, lines 22-24) teach that icIL-1ra-II is mostly intracellular. However, the possibility that icIL-1ra-II is glycosylated cannot be totally excluded.

Furthermore, sIL-1ra, icIL-1ra, and icIL-1raII are different splicing isoforms of the same gene (*IDS*, WO 9612022, April 25, 1996, page 2, lines 13-23 and page 11; also see *IDS* J. Exp. Med. 182:623-628, 1995; left column of page 627). The icIL-1raII protein is identical to icIL-1ra protein except for an additional stretch of 21 amino acids located within the NH2-terminal portion of the molecule. Since sIL-1ra is secreted and thus glycosylated, icIL-1ra remains intracellular, but both of them act as antagonist against IL-1 and are biologically active, glycosylated icIL-1raII is more likely than not to be biologically active.

In view of the teachings in the art, an artisan would reasonably expect the

glycosylated icIL-1raII to be biologically active. Additionally, one skilled in the art would also be able to perform a simple experiment, such as an IL-1 dependent lymphocyte proliferation assay as taught by Pecceu et al. (Section f, page 257), to test whether the glycosylated icIL-1raII is active or not without undue experimentation.

(iv) Applicants argue that the CHO system of Pecceu et al. that is used allows IL-1β to be secreted regardless of whether or not the hGh signal protein is present, it is not clear that it is the human growth hormone signal peptide that causes the secretion of the IL-1β in Pecceu. Thus, it could not be predicted with a reasonably degree of certainty that a protein, such as icIL-1ra-II, which is only expressed intracellularly and is not naturally secreted from the cell, could be made to be secreted in large quantities in a recombinant mammalian expression system when fues to an signal peptide of human growth hormone (bottom of page 12 to top of page 13).

This has been fully considered but is not deemed to be persuasive for the reasons stated in (ii).

(v) Applicants argue that Pecceu et al. report no results as to whether the non-natural glycosylated form of IL-1 creats an immunological reaction when administered to a human or is recognized as cell protein. Bjorkdahl et al. and Muzio et al. supply none of these deficiencies of Pecceu et al. (1st paragraph of page 13).

This has been fully considered but is not deemed to be persuasive for the following reasons. First, Bjorkdahl et al. teach a fusion protein wherein the signal sequence from an IL-1 receptor antagonist was ligated to the cDNA encoding the mature form of IL-1β. Transfection of B16 melanoma cells with the expression vector

encoding the fusion protein results in the secretion of biologically active IL-1β (See, Abstract). The *in vivo* subcutaneous tumor growth of this hybrid IL-1β–tranduced B16 cells in syngeneic C57BL/6 mice was significantly reduced compared with the controls (Abstract). This provides evidence indicating that glycosylated IL-1β is not only biologically active, but also unlikely to cause undesired immunological reactions.

Secondly, the three IL-1 receptor antagonists, sIL-1ra, icIL-1ra, and icIL-1raII are closely related different splicing isoforms of the same gene. The sIL-1ra protein is secreted and thus glycosylated, but it, like icIL-1ra, acts as antagonist against IL-1, providing evidence indicating that lycosylation does not cause immunological reactions.

(vi) Applicants argue that the International Preliminary Examination Report finds that at least claims 2, 6, 8, and 15 are novel and unobvious. The international examiner did not consider the use of the specific human growth hormone signal peptide as being obvious over the prior art (2nd paragraph of page 13 to top of page 14).

This has been fully considered but is not deemed to be persuasive because the International Preliminary Examination Report is only an opinion regarding claimed invention. That opinion does not prohibit this Examiner from examining the case on its merit. Since the icIL-1ra-II protein is known in the art and the art teaches how to produce a secretory protein by fusion of a non-secretory protein with a signal peptide of another secretory protein, it would have been obvious to one having ordinary skill in the art at the time the invention was made to fuse the signal peptide of human growth hormone with the icIL-1ra-II protein to express and to produce the secreted icIL-1ra-II in a host cell with a reasonable expectation of success.

V. Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (703) 306-0282. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Ruixiang Li
Examiner
May 20, 2003

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